REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 30-98 and 100 are in the case.

I. CLAIM AMENDMENTS

Claim 59 has been limited to production of polyhydroxy carboxylate particles having a surface-bound fusion protein that comprises a polymer synthase with an oligopeptide or polypeptide fused to its N-terminus. That oligopeptide or polypeptide may be a binding domain capable of binding one or more biologically active substances or one or more coupling reagents, or it may be at least one biologically active protein, or it may be a combination thereof. The optional section (3) of claim 59 has been presented as new dependent claim 100.

Claims 61 to 71 are withdrawn. However, if possible, the applicant would like to retain claim 64 (in view of this, the status identifier for claim 64 is "previously presented" rather than "withdrawn"). Reconsideration of this aspect of the restriction requirement is respectfully requested.

Claim 81 is now dependent on claim 59, and claims 96 to 98 were withdrawn from consideration following the last restriction requirement. However, it is believed that least claim 97 and claim 98 should be retained since claim 59 is now limited to polymer synthase fusions, and claims 97 and 98 mirror the subject matter of claims 82 to 85. In view of this, the status identifiers for claims 97 and 98 are "previously presented" rather than "withdrawn". Reconsideration of this aspect of the restriction requirement is respectfully requested. Claim 99 has been canceled without prejudice.

II. CLAIM OBJECTIONS

In response to the objection to claim 60, it is respectfully requested that this claim be retained since claim 59 is now limited to the elected subject matter. The objection to the remainder of the claims is also overcome by limiting claim 59 to a polymer synthase fusion protein. Withdrawal of the claim objections is respectfully requested..

III. THE 35 U.S.C. §112, SECOND PARAGRAPH, REJECTION

Claims 59, 60, 72-95 and 99 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The rejection is respectfully traversed.

With regard to the rejection of claim 60, claim 60 has been amended to read "wherein the at least one gene that codes for a protein involved in the formation of polymer particles is selected.. ." This claim language relates to paragraph (A)(3)(b)(i) of claim 59 —now paragraph (b) of new dependent claim 100.

With reference to the phrase "biologically active" in claims 59 and 99, this is supported by the specification. Paragraph [0011] describes what is meant by a "biologically active substance", and paragraphs [0109] to [0113] describe an example where the biologically active substance is the FLAG epitope and is part of a fusion protein. Paragraph [0113] describes an example where the Lac Z protein is the biologically active protein that is part of a fusion protein. Examples 6.1, 6.11 and 6.2 in paragraphs [0104] to [0108] describe chemical modification to add a biologically active

substance. Example 8 in paragraphs [0119] and [0120] describe chemical modification of surface-bound proteins to add binding domains such as biotin.

The term "biologically active protein is intended to encompass any protein that can "initiate a biological response on the part of the organism" including enzymes that "catalyse a specific reaction in the organism" and "proteins, such as for example antibodies" (see paragraph [0011]). The term "biologically active substance" is also intended to encompass any substance that may be bound by a binding domain or a coupling reagent. The terms "binding domain" and "coupling reagent" are discussed in paragraphs [0031] and [0032]. Examples of binding domains capable of binding biologically active substances and/or coupling reagents include oligopeptides, enzymes, abzymes and non-catalytic proteins. Specific examples include FLAG epitopes, cysteine residues and biotin (see paragraph [0031] and paragraphs [0119] to [01203). Examples of coupling reagents are given in paragraph [0039]. Examples of pharmaceutically active ingredients that fall within the phrase "biologically active substance" are given in paragraph [0041]. Examples of other useful proteins are given in [0042]. Biologically active substances may also be pesticides and herbicides (see paragraph [0040]).

In light of the above, it is clear that the phrase "biologically active" would have been clear to one of ordinary skill in this art as of the filing date of the application. Withdrawal of this rejection is respectfully requested.

IV. THE 35 U.S.C. §112, FIRST PARAGRAPH, REJECTION

Claims 59, 60, 72-95 and 99 stand rejected under 35 U.S.C. §112, first paragraph, on alleged lack of description grounds. The rejection is respectfully traversed.

The claims stand rejected as being directed to a method of producing any polymer conjugate comprising any polymeric compound conjugated with any protein or any biologically active substance (any bioactive organic compound or protein) using any host cell expressed with any polymer synthase from any source. In response, and without conceding to the merit of the rejection, the claims have been amended to limit "any protein" to polymer synthase and to limit "any polymeric compound" to hydroxyalkyl carboxylates (see paragraph [00211) by limiting "any polymer conjugate" to polyhydroxyalkyl carboxylates.

In relation to the comment on page 4 of the Action relating to "any biologically active substance", attention is directed to the comments above in relation to the clarity of the term "biologically active". The specification provides sufficient description with regard to this expression to establish that that one skilled in the art would believe that the applicant was in possession of the claimed invention as of the filing date of the application.

In regard to the comment on page 4 of the Action to "any host cell", it is believed that sufficient description on identification and use and production of suitable host cells is given at least in paragraphs [0024] and [0073] to [0120] where the text and the examples describe organisms that are natively able to produce polyhydroxyalkyl

carboxylates or are transformed to adapt them for polyhydroxyalkyl carboxylate production (for example, *E. coli*).

With reference to the comment on page 4 of the Action relating to the claims covering "any polymer synthase from any source", it is noted that the claim is now limited to a polymer synthase that is capable of producing polyhydroxyalkyl carboxylate particles. Suitable polymerases are described in paragraph [0033] and paragraphs [0035] to [0036] that list suitable genera and species. Paragraphs [0084] to [0086] and [0090] describe useful substrate specificity.

With regard to the rejection that the specification fails to describe how any polymer conjugates comprising any polymeric compound conjugated with any protein or biologically active substance (any bioactive organic compound or protein) using any host cell expressed with any polymer synthase [sic], it is not clear what the point is in this sentence in the Action because at least one word appears to be missing. However, the polymer conjugates and polymeric compounds have been limited to polyhydroxyalkyl carboxylate as described above and the applicant is entitled to claim methods for producing constructs that have surface-bound polymer synthases conjugated with any protein or able to bind any biologically active substance where the constructs are produced by any host cell.

The rejection continues on page 4 to reject the claims on the basis that the specification fails to describe in any fashion the physical (structure) and/or chemical properties of the claimed class of polymer particles, protein and biomolecules and their biological function. In response, the polymer particles themselves and the proteins required to produce them are extensively reviewed in Madison (1999) cited in the

Action. Examples 1 though 8 in paragraphs [0073] to [0120] of the present case describe in significant detail the production and use of expression constructs and host cells to carry out the claimed methods.

It is important to note that the claims are not attempting to claim any products. The methods described in the specification provide a person of ordinary skill in the art with everything required to design an expression construct and host cell useful to carry out the claimed method and produce the resulting polyhydroxy carboxylate particles having surface-bound polymer synthase fusion proteins.

The nature of possible polymer synthases capable of producing polyhydroxy carboxylate is discussed in detail in the specification (as noted above). The nucleic acid sequence of suitable biologically active proteins and binding domains may be determined from the literature by any person of ordinary skill in the art. The physical and chemical properties of the polymer particles themselves are described in detail in Madison (1999), and are described in sufficient detail in the specification itself so that a person of ordinary skill in the art would reasonably believe that the applicant had possession of the claimed invention at the time of filing. In addition, as noted above, the specification provides sufficient detail regarding possible biologically active proteins and biologically active substances for a person having ordinary skill in the art to reasonably believe that the inventor had possession of the claimed invention at the time of filing.

The is no requirement to describe the physical and/or chemical properties of all potential biologically active substances, biologically active proteins, binding domains or coupling reagents, because the applicant is not attempting to claim any of these entities *per se*. The claims are directed to a method of producing polyhydroxy carboxylate

particles having surface-bound proteins wherein the method of production employs nucleic acids encoding such proteins or the method itself employs using such proteins, binding domains or substances according to their known properties, many of which are described in the specification, as described in detail above.

On page 4 of the Action, it is stated that a biomolecule can be any molecule. It is not clear what relevance this has to the present case, since the term "biomolecule" is not used in the claims.

The rejection goes on to assert that the specification fails to describe the structure of all polymer particles, biomolecules and proteins. The comments presented above rebut this point.

At page 4 of the Action, it is stated that conjugation of a polymer compound to a protein or a biomolecule depends on the nature of functional groups in those molecules that are to be conjugated. The rejection appears to relate to two features. First, the term "polymer particles" and secondly, the term "fusion protein". The rejection may also relate to the interactions between binding domains and/or coupling reagents and biologically active substances.

In relation to the "polymer particles", the claims have been limited to "polyhydroxy carboxylate particles". Such polymers are described in detail in the specification and examples, and in prior art such as Madison (1999).

In relation to the "fusion protein", the claims are now limited to polymer synthase fusion proteins and the production of polymer synthase fusion proteins is described in detail in the specification at least in Example 6.2.1 in paragraphs [0109] to [0113] and summarized above.

In relation to the interactions between binding domains and biologically active substances or biologically active proteins and interactions between coupling reagents and biologically active substances or biologically active proteins, the applicant is not attempting to claim such constructs *per se*. Rather, the claims are directed to a method of producing polyhydroxy carboxylate particles having surface-bound proteins where the surface-bound proteins comprise such a binding domain capable of binding a biologically active substance or a coupling reagent and where the coupling agent is in turn able to bind a biologically active substance. Many examples of such domains and substances and reagents are given in the specification as described in detail above. Furthermore, many such domains and substances and reagents are reported in the prior art, for example, biotin and streptavidin and antibodies and their complimentary antigens. Many suitable coupling reagents are also described at paragraph [0039] in the specification, as discussed above.

The Action goes on to state that no relationship between the structure of all polymer compounds and proteins is given in the specification. As noted earlier, the claims have been limited to relate to production of polyhydroxy carboxylate particles comprising polymer synthase fusion proteins. The relationship between the polyhydroxy carboxylate polymer particle and polymer synthases is described in detail in the specification including at least at paragraph [0035] to [0036] and in Example 6.2.1 in paragraphs [0109] to [0113].

On page 4 of the Action, the claims are rejected on the basis that the specification does not describe how any host cell can be used to make any polymer conjugate comprising any polymeric compound conjugated with any protein or any

biologically active substance (any bioactive organic compound or protein). In response, the specification provides detailed instructions on using host cells that are natively able to produce polyhydroxy carboxylate particles and also provides a detailed description of how to transform host cells to add the necessary genes to enable cells to produce polyhydroxy carboxylate particles when they are not natively able to do so.

At page 5, beginning at line 5 of the Action, while acknowledging that the specification is enabling for producing any polymer conjugate comprising R-hydroxybutyric acid polymer compound conjugated with FLAG-PhaC1 fusion protein using *E. coli* expressed with plasma pBBad-P containing K. *eutropha* polymer synthase, the Action asserts that the specification does not reasonably provide enablement for a method of producing any polymer conjugates comprising any polymer compound conjugated with any protein or any biologically active substance using any host cell expressed with any polymer synthase from any source. In response, it is believed, for the above discussed reasons, that one of ordinary skill in the art would be able to carry out the invention as now claimed without the exercise of undue experimentation. In particular, the specification provides guidance on:

(1) polymer synthase choice;

(2) choice of biologically active substance or protein;

(3) preparation of expression constructs;

(4) transformation of host cells; and

(5) culturing of host cells.

It is not unreasonable for a skilled worker in this art to conduct experiments to determine that a candidate expression construct results in a fusion protein having the desired binding abilities and the ability to produce polymer particles.

In the middle of page 6 of the Action, the claims are rejected on the basis that the scope of the claims is not commensurate with the enablement provided by the disclosure. In response, it is believed that the invention as now claimed is enabled by the specification.

At the top of page 6, reference is made to lack of guidance, working examples and the unpredictability of the art in predicting the function (polymer synthase activity) from protein structure. In response, the degree of guidance and working examples described above provide sufficient guidance such that a person having ordinary skill in the art would be able to perform the claimed invention without the exercise of undue experimentation. The comments regarding unpredictability of the art in predicting the function of polymer synthases is obviated by limitation in the claims to production of polyhydroxy carboxylate particles and the production of N-terminal polymer synthase fusion proteins.

At the top of page 8, the Action comments on four aspects (A-D) which allegedly evidence that the specification is lacking. With regard to point (A), alleging that regions of the protein structure which may be modified to make polymer particles is not established by the specification, it is noted that the claims are now limited to N-terminal polymer synthase fusion proteins and that discussion of representative polymer synthase fusion proteins is made above, including domains that may be modified without effecting protein function (see paragraph [0035] to [00 36]).

In point (B), it is asserted that the specification does not establish the general tolerance of modification and extent of such tolerance on polymer synthase activity. In response, attention is directed to paragraph [0035] to [0036] which discuss N-terminal fusion. Such fusions are supported by at least Example 6.2.1 and discussed in paragraph [0109] to [01133].

In relation to point (C), it is believed that using the molecular biology tools described in the examples, including the plasmids described, undue experimentation would not be required to determine the possible N-terminal modifications to create fusion proteins that retain polymer synthase activity.

Point (D) appears to summarize the preceding points. It is noted that several polymer synthases of known sequence are available in the art and identifying points at the N-terminus of the protein suitable for continuation of polypeptide chains to produce fusion proteins is well within the skill set of a person having ordinary skill in the art based on the techniques known in the art and the teaching of the specification. Undue experimentation clearly would not be required.

Withdrawal of the formal rejections is now believed to be in order. Such action is respectfully requested.

V. THE OBVIOUSNESS REJECTIONS

Claims 59, 60, 72-95 and 99 stand rejected under 35 U.S.C. §103(a) allegedly unpatentable over Madison *et al.*, Microbiol. Mol. Biol. Rev. 1999, 63, 21-53, or U.S. Patent 6,022,729 to Pieper-furst *et al.* The rejections are respectfully traversed.

Madison describes known PHA biosynthetic pathways and methods for recombinant production of PHA. Madison does not describe production of fusion proteins constructed using proteins involved in PHA synthesis, and does not describe or suggest separation of polymer particles from cultivated cells to produce a composition comprising polyhydroxy carboxylate particles having surface-bound proteins. Madison merely describes production of bulk PHA for use as a bioplastic and conversion into plastic products for consumer use. In view of this, one of ordinary skill would not have been motivated to arrive at the invention as claimed based on Madison. Madison clearly does not give rise to a *prima facie* case of obviousness.

U.S. Patent 6,022,729 is likewise irrelevant. U.S. '729 describes a gene encoding a polyhydroxy alkanoate granule-associated protein designated GA14. U.S. '729 also reports that two C-terminal domains of ten and nine hydrophobic or amphiphilic amino acids respectively are responsible for anchoring GA14 in the phospholipid monolayer of PHA particles (see column 4, lines 13 to 19). U.S. '729 further indicates the use of those domains to produce fusion proteins (see column 4, lines 19 to 21 and column 16, line 48 to column 19, line 23). However, there is no disclosure or suggestion in U.S. '729 of polymer synthase proteins to produce a composition of polyhydroxy carboxylate particles having surface-bound proteins wherein the surface-bound proteins include a fusion protein comprising polymer synthase and a binding domain or biologically active protein or both, as now claimed. Moreover, U.S. '729 does not report that GA14 activity can be retained when GA14 is incorporated in a fusion protein.

The present invention centers on the surprising discovery that polymer synthases are covalently bound to the polyhydroxy carboxylate particle core and cannot be detached from the core either using denaturing reagents such as sodium dodecyl sulfate, urea, guanidium hydrochloride or dithiothreitol, or by using acidic conditions (see paragraph [0035] of the present application). The cited art does not suggest use of polymer synthase fusion proteins, and does not suggest that polymer synthase fusion proteins may be covalently bound to polyhydroxy carboxylate particles providing a more stable construct. Nor is there any suggestion that fusion proteins may be produced using polymer synthase proteins without affecting polymer synthase activity.

In light of the above, it is believed that the obviousness rejections should be withdrawn. Such action is respectfully requested.

Favorable action is awaited.

Respectfully submitted,

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